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Review

Exercise Pills: At the Starting Line

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Sedentary lifestyles, limited physical exercise, and prolonged inactivity undoubtedly increase chronic diseases, including obesity, type 2 diabetes, and cardiovascular diseases. It is widely acknowledged that exercise induces a number of physiological adaptations that have beneficial effects in the prevention and treatment of these chronic metabolic diseases. Unfortunately, exercise compliance is extremely low and often not possible. The development of exercise science and molecular techniques has increased our understanding of the molecular pathways responsive to exercise. Knowledge of these molecular targets has led to the development of chemical interventions that can mimic the beneficial effects of exercise without requiring actual muscle activity. This review focuses on the concept of 'exercise pills' and how they mimic the effects produced by physical exercise including oxidative fiber-type transformation, mitochondrial biogenesis, increased fat oxidation, angiogenesis, and improvement of exercise capacity. We also review candidate exercise pills, and contrast the beneficial effects and molecular mechanisms between physical exercise and exercise pills.

Trends

The concept of 'exercise pills' has great potential for use in patients having low exercise compliance or in those for whom regular exercise is not feasible. Our increased understanding of the molecular targets of physical exercise makes it possible to design agents that mimic the physiological benefits of exercise.

Current candidate exercise pills can be divided into three categories: pharmacological agonists (AICAR, GW501516, GSK4716, SR9009), hormones (MOTS-c, irisin), and phytochemicals [resveratrol and (–)-epicatechin].

The signaling pathways of currently described exercise pills are outlined. None of the candidate exercise pills fully mimics the beneficial effects of exercise, but each exercise pill can activate distinct as well as overlapping target transcriptional regulators that can partly mimic the beneficial effects of physical exercise.

Barriers to Exercise

Developments in technology and resultant changes in working methods have decreased levels of physical exercise and increased time spent sitting, especially in developed countries. Excessive caloric intake and limited physical activity contribute to the current explosion of 'modern' chronic diseases such as obesity, type 2 diabetes, muscle atrophy, and cardiovascular diseases [1–3]. By contrast, regular physical exercise maintains glucose homeostasis and induces physiological adaptations that effectively prevent, and often reverse, these diseases [4–6]. Recognizing the human and economic burdens these diseases cause, and taking into account the health benefits of exercise, have led many exercise scientists to suggest that physical exercise may be the preferred method in the treatment and prevention of these 'modern' chronic diseases [7].

Unfortunately, exercise compliance levels are almost universally low, especially for people using home-based exercise programs, representing a major obstacle to the wide-scale implementation of exercise training methods [8–10]. We knew as early as 1990 when Sluijs and Kuijper [11] reported that while 64% of their patients initially adhered to short-term exercise regimens, only 23% of them sustained this effort over the long term. Moreover, according to the position statement of the study group on exercise training in heart failure of the Heart Failure Association of the European Society of Cardiology, exercise adherence of patients dropped from 84% during the early period of supervised training to 62% 1 year later, and then to 40% 3 years later [10]. In addition, van der Wal *et al.* [12] also report that although 80% of patients recognized the importance of exercise, only 39% of these patients were compliant with the exercise regimens. A variety of factors including poor physical condition, weakness, sickness, lack of time, and poor motivation contribute to low exercise compliance. The much publicized poor compliance begs

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the question: is there an alternative approach that both induces the health benefits of physical exercise and overcomes the problem of low compliance rate?

Mimicking Exercise

Regular physical exercise activates a number of molecular pathways in whole organ systems and reduces the risk of developing numerous chronic diseases (Figure 1A). Although nothing can fully substitute for physical exercise, candidate exercise pills that have emerged in recent years [13–19] may be an attractive alternative for people who are unable to undertake regular exercise because of medical conditions such as obesity, amputations, spinal injuries, metabolic diseases, and musculoskeletal or cardiovascular conditions. The signaling molecules activated by physical exercise are logically considered to be potent pharmacological targets for such exercise pills.

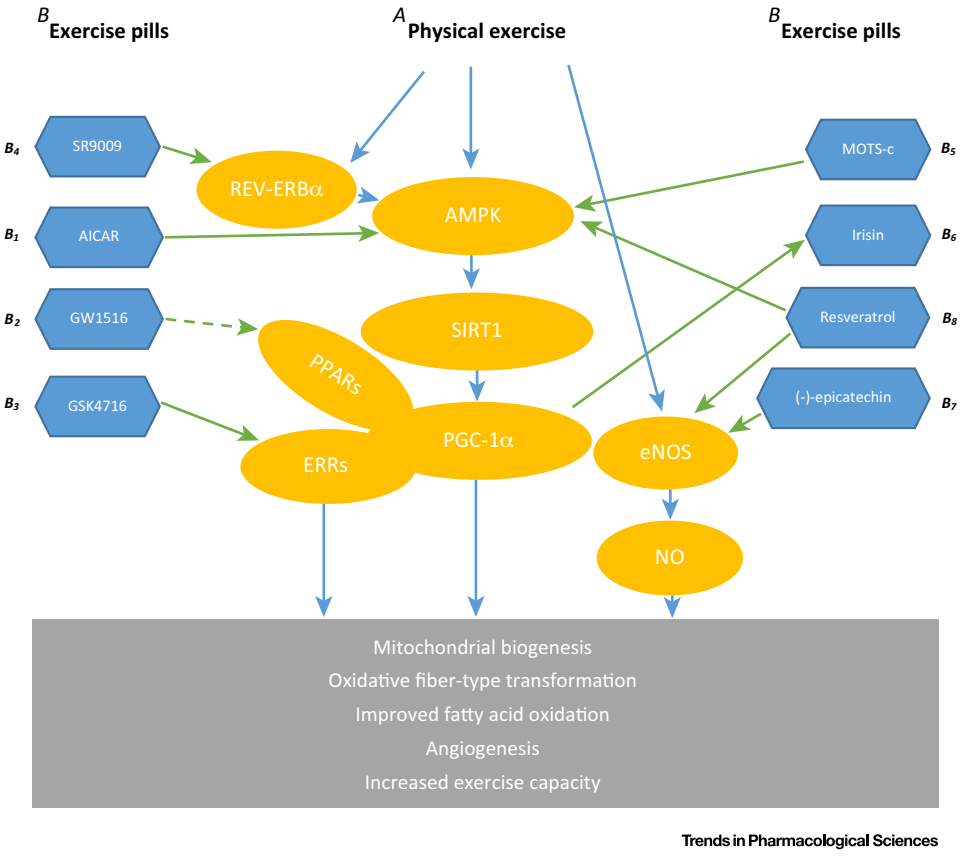

Figure 1. Proposed Molecular Mechanisms and Beneficial Effects of Physical Exercise and Candidate Exercise Pills. The middle panel (A) indicates some molecular pathways activated by regular (conventional) physical exercise and the resultant beneficial effects, such as mitochondrial biogenesis, oxidative fiber-type transformation, improved fatty acid oxidation, angiogenesis, and increased exercise capacity. (B) None of the candidate exercise pills fully mimics the full palette of the beneficial effects of exercise, but each exercise pill can activate distinct as well as overlapping target transcriptional regulators that partly mimic the beneficial effects induced by exercise. Note that GW501516 (B_2) by itself is unable to enhance endurance performance and has synergistic effects when combined with either exercise or AICAR; the combination induces mitochondrial biogenesis and fiber-type transformation and improves exercise capacity. In addition, irisin (B_6), as a PGC-1α-dependent myokine, stimulates browning of white fat, consequently enhancing thermogenesis and total body energy expenditure. Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; SIRT1, silent information regulation T1; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; ERRs, estrogen-related receptors; PPARs, peroxisome proliferator-activated receptors; eNOS, endothelial nitric oxide synthase; NO, nitric oxide.

'Exercise pills' are active compounds that mimic the biochemical and functional effects of regular exercise, such as oxidative fiber-type transformation, mitochondrial biogenesis, improved fatty acid oxidation, angiogenesis, and increased exercise capacity. The concept of 'exercise pills' was first introduced by Himms-Hagen in 2004 [20], followed by Narkar and colleagues [14] who suggested that some molecules could mimic the effects of exercise training. Many subsequent studies have explored the development of exercise pills, and currently described potential exercise pills are listed in Table 1. Next, we briefly discuss the supporting evidence and proposed mechanisms for candidate exercise pills.

Candidate Exercise Pills

AICAR

AICAR, also known as 5-aminoimidazole-4-carboxamide ribonucleotide, AICA-ribonucleotide, ZMP, and acadesine, is an intermediate metabolite in the *de novo* synthesis pathway of inosine monophosphate [21]. It was first used in 1992 as a method of protection against cardiac ischemic injury during surgery [22]. Later, AICAR was developed by PeriCor Therapeutics as an adenosine regulating agent and licensed to Schering-Plough in 2007. Recent data by Narkar *et al.* [14] show that treating mice with AICAR alone for over 4 weeks upregulated gene expression of several proteins involved in oxidative metabolism while also increasing running endurance by 44%. Given this, it seems that AICAR can induce exercise adaptation and increase endurance, even without physical exertion attributable to exercise. Treatment with AICAR for 14 days significantly decreased the proportion of glycolytic fast-twitch (type IIB) myofibers and simultaneously caused even larger increases in the more oxidative and slower-twitch type IIX myofibers in extensor digitorum longus (EDL) muscles [23], indicating that AICAR induces fiber-type transformation in skeletal muscle. This suggests that AICAR could be a promising candidate as an exercise pill.

AICAR, as a synthetic adenosine monophosphate (AMP) analog, can pharmacologically activate AMP-activated protein kinase (AMPK). It is important to note that AMPK is a heterotrimeric complex that consists of catalytic α subunit and regulatory β and γ subunits: exercise activates

Table 1. Current Candidate Exercise Pills

Compound	Category	Target Organ	Molecular Target	Functional Changes	Refs
AICAR	AMPK agonist	Skeletal muscle	AMPK	Fiber-type reformation Mitochondrial biogenesis	[14,21–40]
GW501516	PPARδ agonist	Skeletal muscle	PPARδ	Fiber-type reformation Mitochondrial biogenesis	[14,41–49]
GSK4716	ERR agonist	Skeletal muscle	ERRγ	Mitochondrial biogenesis Fiber-type reformation angiogenesis	[15,50,51]
SR9009	REV-ERB agonist	Skeletal muscle	REV-ERBα	Mitochondrial biogenesis Improved energy metabolism	[18,52–56]
MOTS-c	Mitokine	Skeletal muscle	AMPK	Maintaining metabolic hemostasis Restore insulin sensitivity	[19,57]
Irisin	Myokine	Adipose tissue	PGC-1α	Thermogenesis Enhanced energy expenditure	[17,58–75]
(–)-Epicatechin	Phytochemical	Skeletal and cardiac muscle	NO	Mitochondrial biogenesis Increased capillaries	[16,76–85]
Resveratrol	Phytochemical	Cardiovascular	PGC-1α/NO	Mitochondrial biogenesis Angiogenesis	[13,86–101]

all three subunits depending on intensity [24]. AMPK plays a central role in cellular energy metabolism and is often referred to as the 'metabolic master switch'. It maintains energy balance by promoting cellular uptake of glucose, β-oxidation of fatty acids, and biogenesis of glucose transporter 4 (GLUT4) while concurrently inhibiting ATP-consuming biosynthetic pathways. The energy-sensing capability of AMPK can be attributed to its ability to detect and react to fluctuations in the AMP:ATP ratio, which take place at rest and during exercise [25]. In addition, AMPK is also implicated in the induction of mitochondrial biogenesis [26].

Furthermore, AICAR affects gene expression and regulation. AICAR increases peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) protein levels. PGC-1α is a transcriptional coactivator that induces mitochondrial biogenesis and fiber-type transformation in skeletal muscles [27]. AMPK can directly interact with PGC-1α. Several AMPK-induced mitochondrial gene expression pathways occur through PGC-1α activation [28,29] (Figure 1, compound B_1).

Thus, treatment with AICAR activates AMPK, and AMPK then interacts, either directly or indirectly, with PGC-1α, inducing improved oxidative metabolism, mitochondrial biogenesis, and fiber-type transformation in skeletal muscle. Taken together, this suggests that AICAR is capable of mimicking a broad spectrum of exercise-like adaptation in skeletal muscle.

A new arrival in the exercise mimetic family is compound 14, as reported recently by Asby and colleagues from Southampton University in the UK [30]. Compound 14 is an inhibitor of AICAR transformylase homodimerization and acts differently from treatment with AICAR – this agent increases endogenous levels of AICAR by inhibiting ATIC, leading to a rise in endogenous AICAR and thus activating AMPK and its downstream signaling pathways, including increased fatty acid oxidation and glucose uptake. The detailed study by Asby *et al.* [30] reported that treatment with compound 14 in obese mice for 7 days lowered blood glucose to near normal levels and improved glucose tolerance by approximately 30% while at the same time causing a significant loss of body weight in animals fed a high-fat diet. It is presently unclear if treatment with compound 14 increased exercise capacity or endurance levels in the treated animals.

It is important to note that metformin, widely used in the treatment of type 2 diabetes, is also an AMPK-activating agent. Indeed, metformin lowers blood glucose and enhances insulin sensitivity at least in part through activation of AMPK [31]. Of interest, treating healthy individuals with metformin for 7–9 days slightly but significantly reduced key outcomes related to maximal exercise capacity, such as peak oxygen uptake (VO_{2max}), heart rate (HR), peak ventilation (VE), peak respiratory exchange ratio (RER), and exercise duration [32]. Such findings have since been confirmed in patients with heart failure and lower degrees of insulin resistance [33–35]. The effects of metformin on exercise capacity are complicated by findings that metformin blunts the full effects of exercise training in prediabetic individuals [36], and other findings retort that it modestly reduces the benefits of exercise on glycemic control (by measuring hemoglobin A1c or HbA1c levels) or fitness (aerobic and/or resistance exercise) in an exercise intervention trial. One possibility is that metformin activates AMPK in hepatocytes and consequently reduces acetyl-CoA carboxylase (ACC) activity. Decreased ACC induces fatty acid oxidation and suppresses expression of lipogenic enzymes [31]. Metformin also inhibits complex 1 of the mitochondrial respiratory chain [37–40], but unfortunately inhibition of complex 1 reduces the mitochondrial reserve induced by exercise training and decreases exercise performance [35]. Thus, metformin may not be rightly considered a candidate exercise pill.

GW501516

GW501516 (also known as GW1516, GSK-516, and endurobol) is a peroxisome proliferator-activated receptor δ (PPARδ) agonist originally developed by GlaxoSmithKline (GSK) in 1992.

Initially, GW501516 was used to improve skeletal muscle utilization of fatty acids in preference to carbohydrates, making it a potential treatment for obesity, type 2 diabetes, dyslipidemia, and metabolic syndrome [41–44]. It has since been shown that GW501516 activates PPARδ, thereby inducing physiological adaptations, such as fiber-type transformation, similar to those seen in response to physical exercise. For example, Narkar *et al.* [14] reported that treatment with GW501516 when combined with exercise synergistically increased oxidative slow-twitch (type I) fiber and mitochondrial biogenesis, resulting in improved endurance capacity. However, treatment with GW501516 alone did not alter fiber-type composition, indicating that pharmacological activation of PPARδ by itself is insufficient to enhance exercise capacity.

PPARδ is a member of the nuclear receptor family and plays a crucial role in the transcriptional regulation of skeletal muscle metabolism [45–47]. Exercise training induces its expression in type I fibers of skeletal muscle and triggers type I fiber transformation [45,48,49]. Overexpression of PPARδ leads to mitochondrial biogenesis and high levels of oxidative type I fiber composition [46]. Remarkably, GW501516 and AICAR synergistically affect mitochondrial biogenesis and fiber-type transformation and significantly increase exercise endurance more than either compound alone [14] (Figure 1, compound B_2). More research is needed to better understand the functional consequences of GW501516 and raise its profile as a possible candidate as an exercise pill.

GSK4716

GSK4716 is a synthetic small molecule agonist of estrogen-related receptors (ERRs) and binds to the ERRγ subtype with high selectivity [50]. ERR is a heterotrimeric complex composed of three isoforms: ERRα, ERRβ, and ERRγ. The ERRγ subtype is often described as a key regulator of the oxidative muscle fiber phenotype. It is specifically expressed in slow-twitch muscle types of skeletal muscle and plays an important role in enhancing exercise capacity, activating mitochondrial biogenesis, and controlling angiogenesis and myofibrillar transformation. Recent data show that treatment of mouse myotubules with GSK4716 induced upregulation of ERRγ and its coactivators PGC-1α and PGC-1β by Rangwala *et al.* [15]. By contrast, other findings indicate that structural remodeling and functional improvements induced by ERRγ are independent of PGC-1α, but are related to ERRγ-directed AMPK activation in the muscle (Figure 1, compound B_3) [51]. Clearly, more research is needed to examine this issue in greater detail.

In summary, GSK4716 activates ERRγ to induce myofibrillar transformation, angiogenesis, mitochondrial biogenesis, and improve exercise performance, and can impart several of the benefits accrued by exercise. Thus, it can be considered a candidate exercise pill.

SR9009

SR9009 is a synthetic REV-ERBα agonist developed at The Scripps Research Institute in 2012 [52]. REV-ERBα, also known as NR1D1 (nuclear receptor subfamily 1, group D, member 1), is a member of the REV-ERB family of nuclear receptors [53]. Enhancement of REV-ERBα expression increases mitochondrial content and number, and decreases autophagy flux, thus improving exercise capacity [52,54–56]. Recently, an *in vivo* study found that a single injection of SR9009 induced the expression of genes related to fatty acid catabolism, and enhanced mitochondrial activity; treatment for 12 days enhanced energy consumption without changing the RER, while treatment for 30 days significantly prolonged mouse running times. Additionally, treatment of mouse myocardial cells *in vitro* with SR9009 increased mitochondrial numbers. In contrast to other nuclear receptors such as PPARα, ERRγ, or coregulators such as PGC-1α, treatment with REV-ERBα triggers skeletal muscle mitochondrial biogenesis through modulation of the liver kinase B1(Lkb1)–AMPK-silent information regulation T1 (SIRT1)–PGC-1α pathway, without inducing a switch of muscle fiber types [18] (Figure 1, compound B_4). In addition, REV-ERBα is also a circadian clock component and plays an important role in

regulating rhythmic changes in activity and metabolism. It is likely that SR9009 alters circadian regulation of skeletal muscle activity, leading to increased energy expenditure [52].

Thus, REV-ERBα enhances mitochondrial biogenesis and improves oxidative function. SR9009, a pharmacological agonist of REV-ERBα, may be a promising exercise pill that mimics exercise-like benefits on energy metabolism.

MOTS-c

MOTS-c (mitochondrial open reading frame of the 12S rRNA-c), a hormone encoded in the DNA of mitochondria, was recently discovered by Lee *et al.* [19]. It facilitates accumulation of endogenous AICAR, an AMPK activator. As a mitokine, MOTS-c has systemic effects, but appears to chiefly target skeletal muscle [57]. A recent study indicates that MOTS-c treatment restores insulin sensitivity and metabolic homeostasis in mice fed a high-fat diet [19]. In principle, MOTS-c, as a mitochondrial signaling peptide, acts on the folate cycle in muscle and consistently blocks the tethered *de novo* purine biosynthesis pathway, leading to accumulation of AICAR, AMPK activation, and maintenance of metabolic homeostasis. In addition, MOTS-c also regulates cellular and systemic glucose metabolism and restores insulin sensitivity [19] (Figure 1, compound B_5). To summarize, MOTS-c is a recently identified candidate exercise pill, with a limited profile of detailed studies on exercise capacity. Additional studies are needed to better understand its mechanism in the short and long term.

Irisin

Irisin is a novel myokine first identified by the Spiegelman group [17]. Irisin is secreted by skeletal muscle in response to exercise and targets white adipose tissue [58]. Exercise induces PGC-1α in muscle, and PGC-1α stimulates the expression of fibronectin type III domain-containing protein 5 (FNDC5) genes. The FNDC5 gene encodes FNDC5, which undergoes post-translational processing to form irisin that is then secreted into circulation. Irisin stimulates browning of white fat and increases the expression of uncoupling protein-1 (UCP-1), thereby enhancing thermogenesis and energy expenditure. For example, injection of irisin for 10 days induces weight loss and maintains glucose homeostasis in obese mice [17]. Thus, irisin mimics some important beneficial effects of physical exercise (Figure 1, compound B_6).

Despite a number of recent studies demonstrating that irisin has exercise-like effects, some controversy remains about the claim that irisin is a candidate exercise pill [59–61]. For example, a study by Raschke *et al.* [62] indicated that FNDC5 mRNA expression was not altered in muscle biopsies from human endurance and strength training studies, and questioned whether the beneficial effects of irisin in mice can be translated to humans. Another consideration is that although there are many studies regarding the effects of exercise on human serum irisin levels [63–66], these studies make conflicting claims about the relationship between circulating irisin levels and exercise [67–74]. Many studies used commercially available ELISA kits to examine serum irisin levels that caused Albrecht *et al.* [59] to call into question the accuracy of these data, because when they used western blot analysis with four different antibodies and a sensitive detection system to examine circulating irisin in humans or several animal species, they found unchanged serum irisin levels before and after exercise. In addition, Timmons *et al.* [61] detected no significant increases in FNDC5 mRNA in human muscle biopsies when examined by gene expression arrays after exercise.

A recent follow-up study by the Spiegelman group used state-of-the-art quantitative mass spectrometry (an antibody-independent method) to detect levels of the irisin peptide in human plasma. Circulating irisin levels (~3.6 ng/ml in sedentary individuals) were significantly increased (to ~4.3 ng/ml) by aerobic interval training [75]. Importantly, this study provides fresh evidence that substantiates the earlier report by this group [17]. More research is clearly necessary to

examine this issue in greater detail, with an emphasis on detection methods and levels in acute and chronic exercise of varying levels of intensity.

(–)-Epicatechin

The flavonoid (–)-epicatechin, the most common isomer of epicatechin, is present in plants such as cocoa, tea, and grapes and has been shown to enhance angiogenesis and mitochondrial function both in sedentary conditions and after endurance exercise. One study reported that (–)-epicatechin alone or together with exercise induced structural and metabolic adaptation in skeletal and cardiac muscle and improved endurance capacity [16]. Another study indicated that (–)-epicatechin treatment alone significantly increased mitochondrial signaling, and cumulatively enhanced exercise performance when combined with 8 weeks of exercise training [76]. In addition, (–)-epicatechin may also improve myocardial capillary formation in response to exercise [77].

The beneficial effects of (–)-epicatechin may be attributable to activation of the vascular endothelial growth factor (VEGF)–endothelial nitric oxide synthase (eNOS)–nitric oxide (NO) pathway. Some animal studies demonstrate that (–)-epicatechin increases NO production in endothelial cells [78] and attenuates myocardial injury [79,80]. There are several studies showing that the NO pathway may play a role in mitochondrial biogenesis [81–83] and angiogenesis [84] in skeletal muscle. Remarkably, only (–)-epicatechin, and not the stereoisomers (+)-epicatechin, (–)-catechin, or (+)-catechin, is able to induce *in vivo* capillary formation [85] (Figure 1, compound B_7).

In summary, (–)-epicatechin, as a natural extract, mimics many exercise-like benefits such as improved mitochondrial function and increased capillary formation in skeletal and cardiac muscle, and provides a promising theoretical basis for its potential application as an exercise pill.

Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a naturally occurring polyphenol present in many foods, including red wine, grapes, and blueberries. Resveratrol enhances mitochondrial biogenesis, stimulates angiogenesis, improves exercise capacity, and increases insulin sensitivity in the same manner as exercise training. In animal studies, resveratrol-treated mice had improved mitochondrial function and endurance capacity [13], and resveratrol treatment for 12 weeks induced AMPK expression and ameliorated the whole-body insulin tolerance in KKA^y mice, a model of obese type 2 diabetes [86]. Furthermore, studies in humans show similar adaptations triggered by resveratrol through improvement of mitochondrial efficiency [87,88].

As with exercise training, resveratrol activates the energy-sensing enzyme AMPK [89]. On the one hand, AMPK activation stimulates the NAD^+-dependent type III deacetylase SIRT1 by increasing cellular NAD^+ levels [90,91]. SIRT1 deacetylates PGC-1α and modulates its activity [92,93]. On the other hand, AMPK activation also directly regulates the activity of PGC-1α [94]. Increased PGC-1α triggers gene transcription of nuclear-encoded mitochondrial proteins (NEMPs) and enhances mitochondrial biogenesis [95,96]. In addition, Fukuda *et al.* [97] reported that resveratrol can also stimulate the VEGF–eNOS–NO pathway, which enhances angiogenesis (Figure 1, compound B_8).

However, discrepant results were described by Higashida *et al.* [89] who reported that resveratrol failed to affect mitochondrial biogenesis, despite AMPK activation in skeletal muscle cells. It appears that the inconsistent results of different studies may be related to the differences in the dosage of resveratrol used, as confirmed by several studies showing that dosage plays a crucial role in beneficial effects with resveratrol treatment [13,98,99], and that common resveratrol supplements have levels of resveratrol that are too low to induce changes in mitochondrial properties [100,101]. Thus, further research is necessary to understand the optimal dosage of resveratrol required to induce its exercise-like effects in humans.

Exercise Pills and Vasculature, Epigenetics

While exercise pills arguably can mimic the benefits of exercise in skeletal muscle, their effects in the vasculature are confounded by some important challenges. Exercise increases laminar shear stress in the vasculature to affect multiple signaling pathways (Figure 2), including the phosphoinositide 3-kinase (PI3K), small GTPases such as Ras, extracellular signal-regulated kinase (also known as mitogen-activated protein kinase, MAPK), and NO pathways [102]. Our current understanding is that exercise increases luminal endothelial shear stress, and then mainly activates PI3K to phosphorylate protein kinase B (Akt) and induce Akt-mediated eNOS phosphorylation, leading to higher NO production and its resultant beneficial cardiovascular protective effects. However, of the current list of candidate exercise pills, only (–)-epicatechin and resveratrol activate eNOS expression and increases NO synthesis.

An emerging area of interest is the epigenetic effect of exercise. A recent study in Sweden examined DNA methylation and associated transcriptomic changes in 23 healthy young males and females (average age, 27 years; body mass index, 24 kg/m^2) who were asked to exercise (four times a week for 3 months) on stationary bikes but using only one leg (using an ingenious but simple design whereby the second unexercised leg served as a control) [103]. In addition to the expected physical changes in the exercised leg, there were also almost 5000 sites across the genome with new methylation – with increases in sites related to structural remodeling and glucose metabolism and decreases in those associated with inflammatory/immune responses. Promising preclinical data in rats selectively bred to be high performance runners show that resveratrol can further enhance their performance [104], an effect that may be related to the effects of resveratrol on gene regulation of SIRT1 that increases AMPK phosphorylation [105]. It is unclear if exercise pills can enhance exercise performance in humans and how this may be related to epigenetic regulation of specific genes.

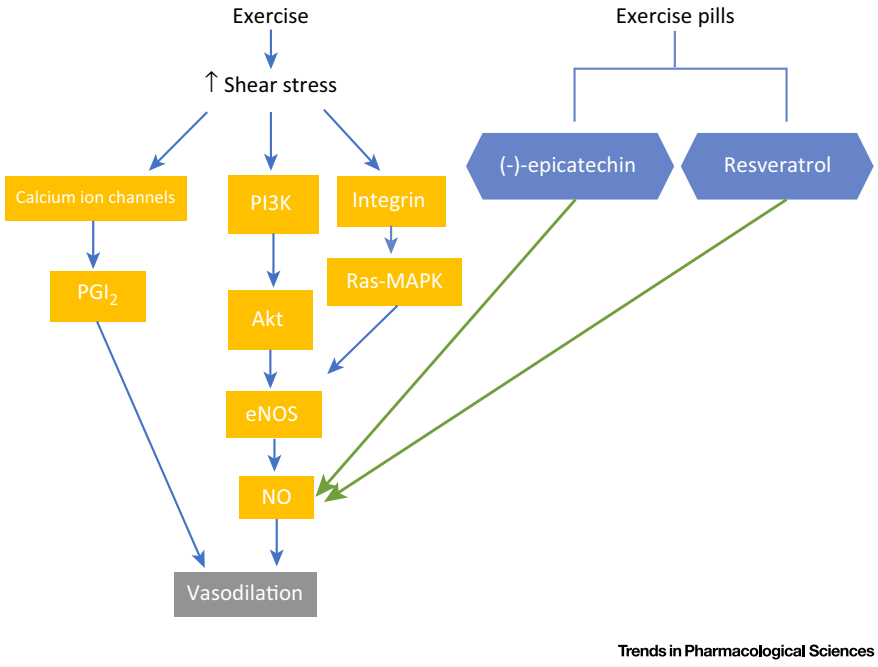

Figure 2. The Possible Molecular Mechanisms of Exercise and Exercise Pills in the Vasculature. Exercise increases laminar shear stress in the vasculature to affect multiple signaling pathways. However of the current list of candidate exercise pills, only (–)-epicatechin and resveratrol activate eNOS expression and increases NO synthesis, mimicking exercise-like beneficial effects. Abbreviations: PI3K, phosphoinositide 3-kinase; Akt, phosphorylate protein kinase B; MAPK, mitogen-activated protein kinase; PGI2, prostaglandin I2; eNOS, endothelial nitric oxide synthase; NO, nitric oxide.

Concluding Remarks

Current candidate exercise pills can be divided into three categories: pharmacological agonists (AICAR, GW501516, GSK4716, and SR9009), hormones (MOST-c and irisin), and phytochemicals [resveratrol and (–)-epicatechin]. Except for the two phytochemicals that are not used to mimic exercise, the other exercise pills are still in experimental stages. For a better understanding of some of these exercise pills, we compared the signaling pathways and physiological adaptation among candidate exercise pills described to date (Figure 3). None of the candidate exercise pills fully mimics the full palette of the beneficial effects of exercise, but each exercise pill can activate distinct as well as overlapping target transcriptional regulators that partly mimic profound beneficial effects in some target organs induced by exercise and enhance exercise capacity (Table 2). Further development of exercise pills that act in combination may be more effective than single compounds.

Many aspects of the current list of candidate exercise pills are still not fully understood (see Outstanding Questions), including side effects, optimal dosage, and misuse. Some studies show that AMPK activation decreases protein synthesis and increases autophagy, resulting in a chronic catabolic state [106,107]. Meanwhile, increased PGC-1α in skeletal muscle induces severe muscle atrophy as mice age [108]. In addition, the first doping case regarding GW501516 was reported in a cycling competition in 2013 [109], thus increasing the need for additional studies on the pharmacokinetics and pharmacodynamics effects of exercise pills in humans.

Remarkably though, exercise pills are still at the starting line and have a long road ahead before they gain clinical application. However, we expect that as we gain an improved understanding of

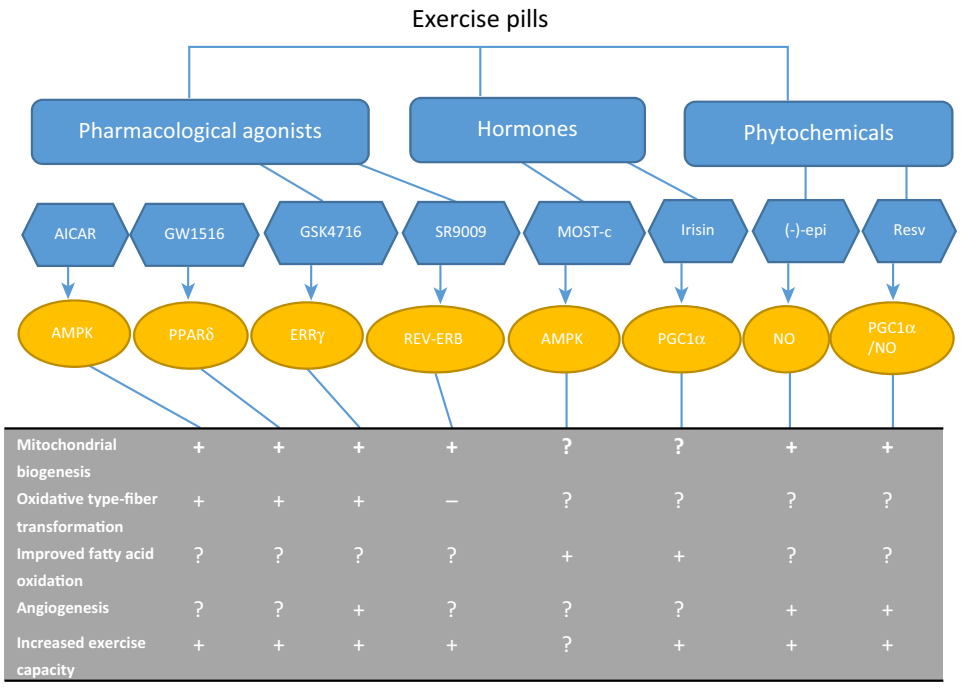

Figure 3. Comparison of Signaling Pathways and Physiological Adaptation among Exercise Pills. Current candidate exercise pills can be divided into three categories: pharmacological agonists (AICAR, GW501516, GSK4716, and SR9009), hormones (MOST-c and irisin), and phytochemicals [resveratrol and (–)-epicatechin]. Each exercise pill can activate specific target transcriptional regulators that partly mimic profound beneficial effects in some target organs induced by exercise. Abbreviations: (–)-epi, (–)-epicatechin; Resv, Resveratrol.

Outstanding Questions

To better understand the therapeutic opportunities available for targeting the molecular targets of physical exercise, the following issues should be more fully addressed when considering exercise pills.

It is apparent that the candidate exercise pills can activate some, but not all, of the molecular pathways stimulated by physical exercise (Table 2). Does this mean that a multidrug approach would be necessary to more fully derive the benefits of physical exercise? For example, aerobic exercise improves cognition in elderly women [110] and also positively impacts cortical neuroplasticity in seniors [111].

Can one achieve the cardiovascular benefits of physical exercise using pharmacological agents that do not increase shear stress on the luminal surface of the endothelium?

Does molecular targeting of signaling pathways stimulated by exercise pills also provide the non-skeletal and non-cardiovascular benefits of exercise such as improved mental health and increased bone strength?

Can the exercise pills currently described be used to extend endurance and performance in physically active people and what are the consequences for 'doping' in professional or amateur sports? Should exercise pills be part of the routine screening tests?

Are there dose-dependent effects with the use of exercise pills and what is the therapeutic index of these agents?

How suitable are the pharmacokinetic properties of currently described exercise pills for long-term use in humans (e.g., dose schedule, oral use, bioavailability, excretion and metabolism in people with pre-existing medical conditions who would otherwise benefit from their use, etc.)? What are the unintended consequences of the long-term use of exercise pills in humans?

Table 2. Comparison of the Target Signaling Activated by Exercise and Candidate Exercise Pills

Signaling	Exercise	AICAR	GW1516	GSK4716	SR9009	MOST-c	Irisin	(–)-Epicatechin	Resveratrol
AMPK	↑	↑	–	↑	↑	↑	–	–	↑
SIRT1	↑	↑	–	↑	↑	↑	–	–	↑
PGC-1α	↑	↑	↑	↑	↑	↑	↑	–	↑
PPARδ	↑	↑	↑	–	–	–	–	–	–
ERRγ	↑	–	–	↑	–	–	–	–	–
REV-ERBα	↑	–	–	–	↑	–	–	–	–
NO	↑	–	–	–	–	–	–	↑	↑

the molecular mechanism by which exercise induces beneficial effects, we will likely gain increased confidence in creating exercise pills that have minimal side effects with much improved efficacy.

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